

NDA 7-073/S-109

Pharmacia & Upjohn Company  
Attention: Gregory A. Brier  
Regulatory Affairs Manager  
7000 Portage Road  
0633-298-113  
Kalamazoo, MI 49001

APR 24 2000

Dear Mr. Brier:

Please refer to your supplemental new drug application dated February 11, 1999, received February 16, 1999, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Azulfidine (sulfasalazine) Tablets and EN-Tabs Tablets.

We acknowledge receipt of your submissions dated February 26, 1999 and January 31, 2000.

This "Changes Being Effected" supplemental new drug application provides for the following revisions to the Azulfidine Tablets (immediate release) package insert: revision of the [ADVERSE REACTIONS section to create a Postmarketing Reports subsection regarding hepatotoxicity](#), in response to our September 1, 1998 letter. Though not identified in the cover letter, the final printed labeling which accompanied the supplement contained numerous additional changes. According to your January 31, 2000 submission, the purpose of these changes was to harmonize the Azulfidine Tablets insert with that of Azulfidine EN-tabs.

We have completed the review of this supplemental application, as amended, and have concluded that adequate information has been presented to demonstrate that the drug product is safe and effective for use as recommended in the submitted final printed labeling (package insert and immediate container and carton labeling submitted February 11 and 26, 1999 [100 count and 300 count, respectively]). Accordingly, the supplemental application is approved effective on the date of this letter.

If a letter communicating important information about this drug product (i.e., a "Dear Health Care Practitioner" letter) is issued to physicians and others responsible for patient care, we request that you submit a copy of the letter to this NDA and a copy to the following address:

MED WATCH, HF-2  
FDA  
5600 Fishers Lane  
Rockville, MD 20857

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We remind you that you must comply with the requirements for an approved NDA set forth under 21 CFR 314.80 and 314.81.

At the next printing of the 100 and 300 count package inserts, please revise the CONTRAINDICATIONS section to read,

“AZULFIDINE Tablets are contraindicated in:

Patients hypersensitive to sulfasalazine, its metabolites, sulfonamides, or salicylates  
Pediatric patients under two years of age,  
Patients with intestinal or urinary obstruction,  
Patients with porphyria, as the sulfonamides have been reported to precipitate an acute attack”

Note: You were requested to make this revision to the EN-tabs insert in a letter dated September 18, 1998. The agency may be notified of this revision in the next annual report.

If you have any questions, call Melodi McNeil, Regulatory Health Project Manager, at (301) 827-7310.

Sincerely,

Lilia Talarico, M.D.  
Director  
Division of Gastrointestinal and Coagulation Drug  
Products  
Office of Drug Evaluation III  
Center for Drug Evaluation and Research

## **Postmarketing Reports**

The following events have been identified during post-approval use of products which contain (or are metabolized to) mesalamine in clinical practice. Because they are reported voluntarily from a population of unknown size, estimates of frequency cannot be made. These events have been chosen for inclusion due to a combination of seriousness, frequency of reporting, or potential causal connection to mesalamine:

**Gastrointestinal:** Reports of hepatotoxicity, including elevated liver function tests (SGOT/AST, SGPT/ALT, GGT, LDH, alkaline phosphatase, bilirubin), jaundice, cholestatic jaundice, cirrhosis, and possible hepatocellular damage including liver necrosis and liver failure. Some of these cases were fatal. One case of Kawasaki-like syndrome, which included hepatic function changes, was also reported.